



Protocol Number: 97-C-0110

Active Accrual, Protocols Recruiting New Patients

Title: Phase I/II Study of Tac-Expressing Malignancies [Other than Adult T-Cell Leukemia (ATL)] with yttrium-90 Radiolabeled Humanized Anti-Tac and Calcium-DTPA

Number: 97-C-0110

Summary: The purpose of the study is to determine (1) the maximum tolerated dose of humanized-anti-Tac monoclonal antibody conjugated with **yttrium-90** (90Y) and (2) the clinical response in patients with Tac-expressing malignancies other than adult T-cell leukemia (ATL). This study represents an extension of Metabolism Branch, NCI protocols utilizing modifications of the anti-Tac monoclonal antibody in the treatment of ATL. The scientific basis for these therapeutic studies is that the malignant cells of patients with various hematologic malignancies express abnormally high levels of the Tac antigen (the IL-2R alpha) on their surfaces whereas resting normal cells, including T cells, do not. The administration of 90yttrium-humanized anti-Tac (90Y-HAT) and intravenous calcium DTPA for patients with ATL is permitted under protocol #96-C-0147. The maximum tolerated dose in the Phase I trial of 90Y-murine anti-Tac (90Y-MAT) (without the intravenous chelate) was 10 mCi. In 1993 a phase II study of **yttrium-90** (90Y)-labeled humanized anti-Tac, also without the chelate, Protocol #93-C-0066 was initiated. In that trial all patients received an initial dose of 10 mCi of 90Y-HAT followed by up to 8 successive doses of 5 mCi. A review of the results of the first 15 patients treated has shown evidence of both less efficacy and less toxicity than seen in the 90Y-murine anti-Tac study. Also, recent data from another group has indicated that the maximum tolerated dose of the 90yttrium can be significantly increased through use of an intravenous chelate, calcium DTPA (Ca-DTPA) to facilitate urinary excretion of 90Y. As a result we proposed and obtained approval for a Phase I/II, dose escalation trial of 90yttrium labeled humanized anti-Tac with a fixed dose of calcium-DTPA for the treatment of patients with Tac-expressing ATL. We seek to redesign the ongoing trial of 90Y-HAT for the treatment of Tac-expressing post-thymic T-cell malignancies [other than ATL] (CC Protocol # 94-C-0068) to include the same modifications and to expand the patient population to include other Tac-positive malignancies. There will be two phases to the study, a phase I dose escalation element to define the maximum tolerated dose and a phase II element at the

maximum tolerated dose of 90Y-anti-Tac defined in the first element.

Sponsoring Institute:

National Cancer Institute (NCI)

Recruitment Detail

Type: Active Accrual Of New Subjects

Gender: Male & Female

Referral Letter Required: No

Population Exclusion(s): None

Eligibility Criteria:

Patients with a histologically confirmed diagnosis of Hodgkin's disease, non-Hodgkin's lymphoma or lymphoid leukemia.

Patients with at least 10% of each patient's malignant cells from peripheral blood, lymph node, skin, or other extranodal sites must react with anti-Tac, as determined by immunofluorescent or immunoperoxidase staining.

Patients with non-Hodgkin's lymphoma (NHL): all histopathologic subtypes of Tac-expressing NHL; indolent NHL stages II through IV if they failed at least one standard therapy and have disease requiring treatment; and relapse after standard chemotherapy and either are not eligible for or have refused salvage chemotherapy or bone marrow transplantation.

Patients with Hodgkin's disease: considered to have a low potential for cure with conventional chemotherapy or radiation therapy; stages II-IV Hodgkin's disease; relapsed or failed to attain a complete remission after first-line chemotherapy; and either not eligible for or have refused salvage chemotherapy or bone marrow transplantation.

Patients with Cutaneous T-Cell Lymphoma (CTCL): all stages of Tac-expressing CTCL, with the exception of stage Ia; stages Ib through III if they have failed at least one standard therapy; and stage IV regardless of whether they have had previous therapy.

Patients with Peripheral T-Cell Lymphoma (PTCL): stages I - IV PTCL; relapsed after first-line chemotherapy and either not eligible for or have refused salvage chemotherapy or bone marrow transplantation.

Patients with lymphoid leukemias or lymphomas not easily classified in the above categories providing they have failed standard therapy and are not eligible for or have refused bone marrow transplantation.

Patients must have a Karnofsky performance status of at least 50.

Creatinine of less than 2.0 mg/dl. An abnormally elevated creatinine must have a creatinine clearance greater than 50 ml/min.

SGOT and SGPT less than 2.5 times the upper limit of normal, bilirubin less than 2.0 unless this is felt to be due to a malignancy.

No clinical cardiac failure; patients with symptomatic pulmonary dysfunction accepted only if it is due to the underlying malignancy.

Granulocyte count of at least 1,500/mm³ and a platelet count of greater than 100,000/mm³.

Patients must be able to understand and sign informed consent.

No breast-feeding females.

Patients with an omission of cytotoxic chemotherapy or other systemic therapy of the malignancy for 3 weeks prior to entry into trial; and patients receiving corticosteroids will not be excluded and must be on a stable dose for at least three weeks before receiving 90Y-HAT on this study.

Patients must have a life expectancy of greater than 1 month.

Patients must be at least 18 years old.

No pregnant female patients or of child-bearing potential.

No HIV antibody positive patients.

No patients with prior history of bone marrow transplant.

No symptomatic disease that is due to malignant involvement of the central nervous system.

No patients with second primary cancer other than basal cell carcinoma of the skin.

No patients receiving chronic anticoagulant therapy.

No patients requiring urgent chemotherapy or radiation therapy for management of their malignancy.

Special Instructions:

Many protocols are potentially hazardous, are intended only for use by clinical oncologists in carefully structured settings, and may not prove to be more effective than standard treatment. A responsible investigator associated with this protocol should be consulted before using this protocol. Dose and schedule modifications are required for patients who develop gastrointestinal, hematologic, neurologic, and biochemical (renal, hepatic, etc.) and/or other abnormalities after the administration of therapy.

Additionally, Federal regulations for the protection of human subjects require approval of clinical trials by your local Institutional Review Board.

Disease Category:
Neoplasms

Keywords:
Non-Hodgkin's Lymphoma
Hodgkin's Disease
Cutaneous T-Cell Lymphoma (CTCL)
Peripheral T-Cell Lymphoma
Radiolabeled Antibody
Monoclonal
Antibody
Radioimmunotherapy

Recruitment Keywords:
None

Investigational Drug(s):
yttrium-90 Humanized Anti-Tac

Investigational Device(s): None

Contacts:
Patient Recruitment and Public Liaison Office, CC.
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Citations:
Waldmann. 1995. Radioimmunotherapy of interleukin-2R-expressing adult T-cell leukemia with yttrium-90-labeled anti-tac. *Blood*, Vol. 86, p. 4063
Hakimi. 1991. Reduced immunogenicity and improved pharmacokinetics of humanized anti-tac in cynomolgus monkeys. *J Immunol*, Vol. 147, p. 1352
Pinkus. 1990. Peripheral/post-thymic t-cell lymphomas: a spectrum of disease: clinical, pathologic, and immunologic features of 78 cases. *Cancer*, Vol. 65, p. 971

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If you have:

- Questions about participating in a study, please contact the Patient Recruitment and Public Liaison Office, CC.

- Questions about specific studies, or the database in general, please contact the Protocol Coordination Service Center, CC.
- Technical questions regarding the Clinical Center web site, please contact the Information Systems Department, CC.

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J Immunol 147: 1352-1359 (1991)[PMID:1869828, MUID:91332449]

Reduced immunogenicity and improved pharmacokinetics of humanized anti-Tac in cynomolgus monkeys.

J. Hakimi, R. Chizzonite, D. R. Luke, P. C. Familletti, P. Bailon, J. A. Kondas, R. S. Pilson, P. Lin, D. V. Weber, C. Spence & ...

Department of Immunopharmacology, Hoffman-La Roche, Inc., Nutley, NJ 07110.

The anti-Tac mAb has been shown to bind to the p55 chain of the IL-2R, block IL-2 binding and inhibit T cell proliferation. A humanized form of anti-Tac (HAT) has been constructed that retains the binding properties of murine anti-Tac (MAT). These two mAb were evaluated in cynomolgus monkeys to compare relative immunogenicity and pharmacokinetic properties. Monkeys treated with HAT daily for 14 days exhibited anti-HAT antibody titers which were 5- to 10-fold lower than their MAT-treated counterparts and these antibodies developed later than in the MAT-treated monkeys. Two of four monkeys receiving a single injection of MAT developed anti-MAT antibodies, whereas none of four monkeys developed antibodies after a single treatment with HAT. In monkeys injected with either HAT or MAT daily for 14 days, the anti-antibody titers induced were inversely related to the amount of anti-Tac administered. Antibodies that developed against MAT were both anti-isotypic and anti-idiotypic, whereas those developed against HAT appeared to be predominantly anti-idiotypic. The pharmacokinetic properties, that is the half-life and area under the curve values, of HAT were also significantly different from those of MAT. The area under the curve values for HAT in naive monkeys were approximately twofold more than those for MAT, and the mean serum half-life of HAT was 214 h, approximately four- to fivefold more than MAT. These pharmacokinetic values were reduced in monkeys previously sensitized with HAT or MAT suggesting that the presence of anti-antibodies altered these parameters.

Comments and questions to the [Help Desk](#)

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